AP/1621$ JFW

# U.S. DEPARTMENT OF COMMERCE
# PATENT AND TRADEMARK OFFICE

## AMENDMENT TRANSMITTAL LETTER

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| | | Docket Number: **01662/054902** | |
| Application Number **10/045,510** | Filing Date **October 19, 2001** | Examiner **Samuel A. Barts** | Art Unit **1621** |
| Invention Title **CRYSTALLINE VENLAFAXINE BASE AND NOVEL POLYMORPHS OF VENLAFAXINE HYDROCHLORIDE, PROCESSES FOR PREPARING THEREOF** | | Inventors **Dolitzki et al.** | |

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Date: May 15, 2006

Signature: _____

Sir:

1. Transmitted herewith for filing is an Amendment in response to the Notification of Non-Compliant Appeal Brief mailed April 18, 2006 for the above-identified application. A response to which is due on May 18, 2006.

2. It is believed that no fees are due in connection with this paper. However, should any fees be due the Commissioner is authorized to charge deposit account number **11-0600** for such fees.

Respectfully submitted,

Date: May 15, 2006

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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|---|---|
| In re Application of: Dolitzki et al.<br>Application No.: 10/045,510<br>Filed: October 19, 2001 | Art Unit : 1621<br>Examiner : Samuel A. BARTS |

For: CRYSTALLINE VENLAFAXINE BASE AND NOVEL POLYMORPHS OF VENLAFAXINE HYDROCHLORIDE, PROCESSES FOR PREPARING THEREOF

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Date: May 15, 2006

Signature: Chandra Sekaran

## AMENDED APPEAL BRIEF

Appellants respectfully submit this Amended Appeal Brief pursuant to 37 C.F.R. § 41.37 in response to the Notification of Non-Compliant Appeal Brief mailed April 18, 2006.

Appellants filed an Appeal Brief on February 1, 2006. The Amended Appeal Brief removes the section entitled "Grouping of Claims" and amends the section heading "Summary of the Invention" to recite "Summary of Claimed Subject Matter." No further changes have been made.

### REAL PARTY IN INTEREST

The real party in interest for U.S. Patent Application Serial No. 10/045,510 is:

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P.O. Box 3190
Petah Tiqva 49131
Israel

## RELATED APPEALS AND INTERFERENCES

There are no other prior or pending appeals, interferences or judicial proceedings known by the undersigned, or believed by the undersigned to be known to Appellants or the assignee, "which may relate to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal."

## STATUS OF CLAIMS

Claims 1, 2 and 95-98 are pending. Claims 3-94 have been withdrawn from consideration. Claims 1-2 and 95-98 are under rejection and on appeal. Text of the pending claims is provided in the Claims Appendix.

## STATUS OF AMENDMENTS

An Amendment under 37 C.F.R. §1.116 was filed June 27, 2005 requesting reconsideration of the pending claims but was not entered.

## SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter of the present invention relates to white crystalline venlafaxine and venlafaxine prepared by a method of the invention. Venlafaxine has the chemical formula (±)-1-[2-(Dimethylamino)-1-(4-ethyoxyphenyl) ethyl] cyclo-hexanol. For the purposes of this appeal, the claims have been divided into two groups:

1) Independent claim 1 and dependent claim 2 directed to venlafaxine in white crystalline form; and

2) Independent claim 95 and dependent claims 96-98 directed to venlafaxine prepared by processes recited therein.

Venlafaxine in white crystalline form (Group 1) is disclosed in the specification, for example, on page 2, lines 7-9 as well in on page 6, lines 9-11 and also in Example 1, page 7, line 9. A powder x-ray diffraction pattern of crystalline venlafaxine base is provided in Figure 9 as described in page 5, line 24 of the specification.

Venlafaxine prepared by a method of the invention (Group 2) is disclosed, for example, on page 6, lines 12-18 of the specification. The claimed method is also described in Example 1, page 6, line 28 to page 7, line 10.

Groups 1 and 2, claims 1, 2 and 95-98, stand or fall together.

## GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1 and 2, which stand rejected under 35 U.S.C. § 103, are *prima facie* obvious in view of WO 00/32555.

Whether claims 95-98, which are product-by-process claims rejected under 35 U.S.C. § 103 are *prima facie* obvious in view of WO 00/32555.

## ARGUMENT

**Rejection under 35 U.S.C. § 103 over WO 00/32555**

Claims 1, 2 and 95-98 stand rejected under 35 U.S.C. § 103 as *prima facie* obvious over WO 00/32555 ("the '555 publication," attached hereto as Exhibit 1). *See* August 1, 2005 Advisory Action. These claims are directed to venlafaxine base "in the form of white crystals." The '555 publication discloses venlafaxine base as a "yellow gum that turned slowly in to [*sic*] a pale yellow solid." The '555 Publication, p. 23, line 24.

## A. A Colorless (White) Form of a Known Compound is not Prima Facie Obvious Over a Colored (Yellow) Form of the Compound

1. Background

Patentability of Applicants' claims does not turn on the purity of their venlafaxine base ("venlafaxine") alone. The Office acknowledges that Applicant's invention is not directed to the mere purity of venlafaxine, but to a difference in both color and crystallinity. *See* December 28, 2004 Office Action, p. 2.

But in rejecting Applicants' claims to white crystalline venlafaxine over the yellow solid of undisclosed crystallinity in the '555 publication, the Office mistakenly equates color with general purity, discussed *infra*, alleging that "Applicant has done nothing to make the crystals white other than purifying venlafaxine base." *Id.* The Office further states that "color is simply an inherent property" of purity, and that "mere purity of compound, in itself, does not render a substance unobvious." *Id.*

It is clear that the Office has rejected the claims on appeal as *prima facie* obvious on the ground that white crystalline venlafaxine is merely a more pure form of a known compound. Applicants hereby argue accordingly.

2. Proper Application of the Prescript of M.P.E.P. § 2144.04 VII[1] that Mere Purity Does Not Render Patentable a Purer Form of a Known Compound Requires that "Purity" be Construed as "General Purity" or "Assay"

"Purity" does not have an immutable definition. The different connotations for the term "purity" in the chemical and allied arts is succinctly summarized by BASF Aktiengesellschaft, The Chemical Company, in its Frequently Asked Questions (FAQ):

> What exactly is purity? Most people would define purity by the actual content of the desired compound expressed in weight percent . . . **Weight % is only one of many possible definitions of purity**. A catalysis chemist would define purity as being **free of** any coordination species, like halides which deactivate the metal by formation of stable complex compounds. An electrochemist would define purity by **having no oxidisable impurities** which narrow down the electrochemical window. An engineer might prefer not to have impurities that affect the viscosity and finally the end user will define purity as being **free of** residual potentially toxic alkylating agents. These examples show, that only the targeted application defines what purity in this case means.

*BASF Aktiengesellschaft* FAQ, http://www2.basf.de/en/intermed/nbd/products/ionicliquids/faq.htm?id=V00-cK1th82Yqbw22XQ#2c, p. 3 (emphases added) (attached hereto as Exhibit 2).

The conflict between the different uses of the term "purity" is also acknowledged by the chemical company Fisher Scientific International, which in its product literature Frequently

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[1] "Pure materials are novel *vis-à-vis* less pure or impure materials because there is a difference between pure and impure materials. Therefore, the issue is whether claims to a pure material are unobvious over the prior art. *In re Bergstrom*, 427 F.2d 1394, 166 USPQ 256 (CCPA 1970). Purer forms of known products may be patentable, but the mere purity of a product, by itself, does not render the product unobvious. *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989).

Factors to be considered in determining whether a purified form of an old product is obvious over the prior art include whether the claimed chemical compound or composition has the same utility as closely related materials in the prior art, and whether the prior art suggests the particular form or structure of the claimed material or suitable methods of obtaining that form or structure. *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) (Claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals.).".

Asked Questions lists several types of purity standards, both general and specific, that chemical manufacturers adhere to. *See Fisher Scientific International* FAQ, https://www1.fishersci.com/support/ faq/faq_chem.jsp (attached hereto as Exhibit 3). Recognizing that general purity (% assay) is most often what is meant when "purity" is used, Fisher Scientific International recommends that "[w]hen referring to the 'purity' of a product, it is better to use the term 'assay.'" *See id.* at 7.

"General purity" – or assay – is expressed as total weight percent of a principal compound in a sample (*e.g.*, 90% assay). Another connotation of purity, which Appellants refer to as "specific purity," refers to an amount of a particular and typically undesired impurity in the principle compound (*e.g.*, 1% impurity A in the principal compound). Thus, the catalysis chemist and the electrochemist referred to in the BASF FAQ, *supra*, are in Appellants parlance concerned with specific purity – freedom from oxidizable substances for the electrochemist or catalyst poisons for the catalysis chemist. Thus, a sample can have a lower general purity but higher specific purity (*e.g.*, 60% assay, 0.1% impurity A), or vice-versa (*e.g.*, 95% assay, 5% impurity A).

In arguing the rejection, the Office ostensibly relies on the prescript, incorporated in M.P.E.P § 2144.04, that mere purity of a product, by itself, does not render the product unobvious. Appellants vigorously assert that proper application of this prescript in support of a rejection of a claim as *prima facie* obvious requires that "purity" be construed in the sense of "general purity" or assay.

One skilled in the chemical arts is well aware that certain classes of organic compounds, for example dyes and biological stains, have very large extinction coefficients in the visible region of the spectrum. A little bit – a "trace amount" – of such a compound – call it compound

"A" – can go a long way to colorizing a sample of a compound, even a sample having a very high assay. When specific purity – the presence of one or more specific impurities – is the issue, slavish improvement in assay does not create a reasonable expectation that the kineticist's catalyst poison, the electrochemist's oxidizable compound, or the organic chemist's colorizing substance will be removed.

Applying the prescript that a more pure form of a known compound is *prima facie* obvious to reject a claim to the more pure compound – in the specific sense – would be tantamount to denying a claim to one who first removes the electrode-fouling oxidizable material, the catalyst poison, or the colorizing impurity from the respective substance, even such removal (or reduction) resulted in only a *de minims* improvement in assay. *See, e.g., In re Sponnoble*, 405 F.2d 578, 585 (C.C.P.A. 1969) ([A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103.).

The Office acknowledges that Applicants' claims are not directed to the mere purity of venlafaxine. But the Office rejects the claims alleging that all Applicants have done is to purify venlafaxine. *See* December 28, 2004 Office Action at page 2. Even assuming, *arguendo*, that there *might* be differences in purity between the white crystalline venlafaxine of Applicants' claims and the yellow venlafaxine of undisclosed crystallinity taught by the '555 publication, the Office has not presented any discussion or argument that the differences are differences in assay,

which might support a rejection for *prima facie* obviousness, and not differences in specific purity, which Applicants urge cannot not support such a rejection[2].

3. The Office Erroneously Equates Color and General Purity or Assay

The Office rejects the claims on appeal as *prima facie* obvious. Advisory Action of August 1, 2005. In making the rejection, the Office implicitly equates color and purity, in the sense of general purity or assay, which Applicants have asserted is the only construction of "purity" consistent with the prescript that "mere purity" does not bestow patentability to a claim to a known compound. But color is not a surrogate for purity.

Applicants have already explained why one skilled in the chemical arts knows that purity (assay) and color do not go hand-in-hand. Many practical examples demonstrate this point.

A well-known example of how two compounds with the same general purity can have markedly different colors because of specific impurities is the sapphire-ruby comparison. Both sapphire and ruby are a form of corundum, which "is colorless in its pure state." *AJS Gems Gem Library*, www.ajsgems.com/GemLibrary/Ruby.htm (attached hereto as Exhibit 4). Sapphire is deep blue because of the presence of the impurities iron and titanium. Ruby is traffic-light red because of the presence of chromium as an impurity. For these gems, if the specific color-inducing impurities are not removed, the gems can be purified to the highest assay possible, yet still never be colorless like corundum.

"Different kinds of impurities can produce a wide range of color even in the same crystal structure." Gordon et al., *Crystals*, The Natural History Museum, p. 13 (2004) (attached hereto as Exhibit 5). As illustrated by sapphire and ruby, differences in color do not unquestionably

[2] Applicants point out that "pure" or "purity" have yet a third connotation in the sense of isolated. A pure (read isolated) form of a compound hitherto only known in mixtures is patentable. *In re Kratz*, 592 F.2d 1169 (CCPA 1979).

depend on general purity (*e.g.*, purifying from 95% to 99%), but can depend on the presence or absence of specific trace impurities. The reasoning applied by the Office would lead to rejection of a claim to blue corundum as *prima facie* obvious in view or red corundum.

That a specific trace impurity, rather than general purity as reflected in an assay, can be responsible for the color of a compound is still further demonstrated by the known but not-yet-fully-understood propensity of paroxetine hydrochloride to exhibit a pink color. According to Avrutov et al., WO 02/102382, which describes a process for preparing paroxetine hydrochloride substantially free of pink-colored compounds, "it is believed that impurities in paroxetine hydrochloride play a role in the color change to pink." WO 02/102382, p. 2, ¶ 1 (attached hereto as Exhibit 6). This publication discusses the effect of a specific impurity on color:

> [One] approach is to measure the degree of **an** impurity identified by a high pressure liquid chromatography ("HPLC") relative retention time ("RRT") of about 1.5. The different UV-spectrum characteristic of **this impurity** has linked the impurity to the development of a pink color. A color change however can occur even if this impurity is present at low levels, suggesting that other impurities may also play a role in the change in color. Purification steps to remove this impurity such as by crystallization, extraction, chromatography or other sepraration procedures are often ineffective.

(emphases added). *Id.*

The chemical company BASF Aktiengesellschaft also addresses the relationship between color and specific impurity content in compounds known as "Ionic Liquids" which, like paroxetine hydrochloride, are susceptible to color change due to the presence of specific color-causing impurities:

> Colored materials are quite often perceived as being impure. In fact, most Ionic Liquids are colorless liquids. However, they tend to become colored especially during prolonged thermal treatment. The good news is that the color persistently stays in the Ionic Liquid and cannot be extracted in any organic product or solvent.

> Currently no one has managed to isolate the colorant because the **quantities are just too low**. It is assumed that oligomers of the imidazole or even radical ions might cause the color.

*BASF Aktiengesellschaft* FAQ, p. 4 (emphasis added).

4. Crystallinity Alone, and Not General Purity or Assay, may Dictate a Compound's Color

The myth that color is merely a surrogate for purity is further debunked by the fact that crystallinity, not purity, of a compound can be dispositive of its color. A famous example of how the color of a compound is determined by its crystalline form is N-(2'-nitrophenyl)-2-amino-3-cyano-5-methyl thiophene, also known as "ROY." This compound earns its name ROY from the fact that its three crystalline forms dictate whether the compound will be red, orange, or yellow. Smith et al., *Application of Two-Dimensional 13C Solid-State NMR to the Study of Conformational Polymorphism*, J. AM. CHEM. SOC., 11710-11713 (1998) (attached hereto as Exhibit 7). That three crystalline forms of the same compound having the same polymorphic (general) purity exhibit three different colors not because of purity but because of **different crystal structure** is still further demonstration that color is **not** a surrogate of purity.

As the Office acknowledges, Applicants do not claim venlafaxine of a different purity. The Office attempts to circumvent with this acknowledged fact by equating, *sub silentio*, color (in this case lack thereof) and purity (assay). The forgoing discussion amply demonstrates the fallacy of this position.

The Office agrees that the difference between the venlafaxine disclosed in the '555 publication and the white crystalline venlafaxine of the claims on appeal is the color of Applicants' venlafaxine. Because color is not *ipso facto* a proper surrogate for purity in any sense, there is no basis for the Office's assertion that Applicants have done nothing more than to purify venlafaxine.

**B. A Stable White Crystalline Material is not *Prima Facie* Obvious over a Yellow Gum that Solidifies upon Standing**

Applicants' case is similar to that of *In re Cofer*, 354 F.2d 664 (C.C.P.A. 1966) (attached hereto as Exhibit 8). There, the issue was whether applicant-appellants' claimed product "2,2-B" which was free-flowing and in crystalline form, was obvious in light of cited references disclosing the same compound as a viscous liquid. *In re Cofer*, 354 F.2d at 666. The references cited by the examiner taught that 2,2-B was either "water white" or "amber." *Id.* Appellants pointed to the various advantages of its crystalline product as compared to the prior art such as, for example, "better color, high epoxy content, lower impurity content, and easier to handle . . . ." *Id.* at 666-667. The examiner asserted in the Answer that the appellants' claims "are directed to a more pure form of the disclosed compound which has been made to crystallize and is claimed in its crystalline form as a manufacture." *Id.* at 666.

Reversing the Board's decision which affirmed the obviousness rejection, the court held that the record failed to support the conclusion that those skilled in the art should have known that 2,2-B would exist in crystalline form, or that it would be known how to obtain such crystals. The court stated its reasons as follows:

> There is no explanation in the views of the board or examiner why it should be found from the references or from common knowledge that a person skilled in the art would regard free-flowing crystals of 2,2-B to be obvious. In such circumstances, we are not free to search for speculative reasons that might support the rejection, when it is apparent from those opinions that [the references] were ultimately used only to show that 2,2-B was **known as a viscous liquid**, and not to suggest that the **crystalline** form would also exist.

*Id.* at 667 (emphases added).

The court found that the Board had "failed to address itself to factors which must be given weight in determining whether the subject matter as a whole would have been obvious,

namely, whether the prior art suggests the **particular structure or form** of the compound or composition as well as suitable **methods of obtaining** that structure or form." *Id.* at 668 (emphases added). In reaching its decision, the court rejected the Board's proposition that "merely changing the form, purity or another characteristic of an old product . . . does not render the claimed product patentable[3]." *Id.* at 667.

*Cofer* is directly on point. Applicants' claims are directed to a crystalline white venlafaxine. The '555 publication teaches that venlafaxine is instead a yellow gum which, after some undisclosed period of time, eventually "turned slowly in to pale yellow solid." '555 Publication, p. 23, line 24. Applicants are the first to have successfully produced venlafaxine as a white crystalline solid, which, like the 2,2-B in *Cofer* but especially in view of its use in pharmaceuticals, provides significant advantages in color, form, and purity. Applicants have explained in their prior submissions that crystals are typically preferred over gums, which are much more difficult to manipulate in practice, especially in manufacturing. *See, e.g.*, June 27, 2005 Amendment, p. 13. Moreover, the transformation from gum to solid upon sitting for an undisclosed time strongly suggests that the product of the '555 publication is unstable. The Office's position, like that of *Cofer*, is simply that "mere purity of compound, in itself, does not render a substance unobvious." December 28, 2004 Office Action, p. 2.

The same deficiency in *Cofer* is found here, where the cited reference '555 publication does not teach or suggest whiteness or crystallinity of venlafaxine let alone suitable methods of obtaining such venlafaxine. The reference ultimately shows only that venlafaxine was known as

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[3] The Court distinguished from *Ex Parte Hartop*, 139 U.S.P.Q 525, stating that "[n]ecessarily **it is facts appearing in the record, rather than prior decisions** in and of themselves, which must support the legal conclusion of obviousness under 35 USC 103." *Id.* "We see no need to review the cases relied on there save that each case must stand on its own facts." The court further noted that "[t]he cited cases fail to support the broad proposition" advanced by the Board. *Id.* (emphasis added).

a yellow gum that eventually turned into a solid, and cannot be said to suggest that the white crystalline form would also exist. *See In re Cofer*, 354 F.2d at 667. The Office has "failed to address itself to factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the **particular structure or form** of the compound or composition as well as suitable **methods of obtaining** that structure or form." *See id.* at 668 (emphases added).

*Cofer* rejected the Board's reliance "on the discussion of prior case law in *Hartop*" to reach its conclusion that "the question whether appellant's product had the same or different utility [was] dispositive of the issue here . . . ." *Id.* at 667. The court stressed that whether a chemical compound has the same utility as a closely related material "is only one consideration" in determining obviousness. *Id.* To this end, Applicants respectfully submit that not only is its novel white crystalline compound (and method of its production) not suggested anywhere in the '555 publication, but it further has better utility as a white crystal over a yellow gum. A more advantageous visual appearance which improves the marketability of a product is a utility recognized by the Federal Circuit in assessing patentability. *See Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1367 (Fed. Cir. 1999). The majority of consumers and pharmaceutical manufacturers would much prefer white crystalline venlafaxine instead of a yellow gum that may later solidify after an unknown amount of time. Therefore, the white crystalline appearance of venlafaxine is an additional utility and improvement over the yellow gum of the '555 publication.

**C. The '555 Publication Teaches Away from a White Crystalline Form and the Obviousness Rejection is Improperly Based on Hindsight**

At the time of Applicants' invention, the disclosure of the '555 publication that venlafaxine existed as a yellow gum which eventually turned into a solid after an undisclosed

period of time, would have discouraged the skilled artisan from attempting to obtain venlafaxine as a crystalline solid. As mentioned above, the skilled artisan would have recognized that "gums" were inherently unpredictable. One could not have known if or when a transformation of the product disclosed in the '555 publication to a white crystalline solid would occur, or whether the solid would turn back into a gum again. Moreover, Applicants submit that after the solvent is removed in Example 1 of the '555 publication, the yellow venlafaxine gum remains in the reactor vessel, where it slowly solidifies. Because this gum cannot be isolated, it cannot be filtered or processed any further in the hopes of obtaining a different form of venlafaxine, *e.g.* as a white crystal. The '555 publication eviscerates any reasonable expectation that the skilled artisan of the day might have harbored that venlafaxine could exist as a white crystalline solid.

Because the reference teaches venlafaxine (base) as a yellow gum which later unpredictably solidifies, and further because this gum remains in the reactor vessel and is not removed, the skilled artisan seeking to produce a pharmaceutical salt (such as venlafaxine hydrochloride) from the base venlafaxine would be dissuaded from the additional step of isolating the pure base, and would try instead to obtain the hydrochloride salt directly from the gum/solid. Therefore, Applicants assert that the '555 publication teaches away from producing venlafaxine as a white crystal.

The Office also failed to provide a reasonable expectation of success. The mere fact that Applicants, through their diligent efforts in the face of the discouraging teachings of the '555 publication, persevered and discovered white crystalline venlafaxine and its preparation, is not grounds to say, today, that it was obvious this could be done. Such a reliance on hindsight to establish a case of obviousness is improper. *See Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 (Fed. Cir. 1986) ("the references must be viewed without the benefit of hindsight vision

afforded by the claimed invention"). The Office is obligated to provide specific references that teach or suggest the white crystalline form, including methods of obtaining these white crystals, instead of using applicant's disclosure to meet its burden of proof. *See In re Irani*, 57 C.C.P.A. 1109, 1113 (C.C.P.A. 1970). "Even assuming that one skilled in the art could have predicted with reasonable certainty that crystalline [form] could be produced," there must be a showing that "it would also have been obvious **how** this could be achieved." *Id.* at 1113 (emphasis added).

The '555 publication teaches away from a white crystalline form of venlafaxine. The Office has improperly used Applicants' discovery of white crystalline venlafaxine to assert that, because Applicants did it, it was obvious to the skilled artisan of the day to do it and how it could be done.

**D. The Examiner has Improperly Taken Official Notice by Equating Color with Purity**

Applicants have amply demonstrated, from the foregoing examples, that color is in no way an indicia or "inherent property" of general purity. Moreover, not only is the Office's mistaken presumption factually incorrect, but it is further legally flawed.

The Office's rejection of Applicants' claims is procedurally deficient because it has improperly taken official notice in assuming an inherent nexus between color and general purity and that Applicants' white venlafaxine crystal is simply a purer assay of the yellow solid disclosed in the '555 publication.

The Manual of Patent Examining Procedure (MPEP) proffers extensive guidance "to assist the examiners in determining when it is appropriate to take official notice of facts without supporting documentary evidence or to rely on common knowledge in the art . . . ." *MPEP* § 2144.03. The MPEP clearly states that official notice, unsupported by documentary evidence,

should only be taken where the facts asserted to be well-known are "capable of such **instant and unquestionable demonstration as to defy dispute**." *In re Ahlert*, 57 C.C.P.A. 1023, 1027 (C.C.P.A. 1970) (emphasis added). "If the Patent Office wishes to rest a rejection on **chemical theory, it is its duty to support its case** with adequate evidence of the existence and meaning of that theory." *In re Mills*, 281 F.2d 218, 223-24 (C.C.P.A. 1960) (emphasis added) ("The position of the board is predicated on nothing more than the 'legal presumption' as authority for which it cites [another] case."). "Assertions of technical facts in areas of esoteric technology must always be supported by citation to some reference work recognized as standard in the pertinent art and the appellant given, in the Patent Office, the opportunity to challenge the correctness of the assertion or the notoriety or repute of the cited reference." *In re Ahlert*, 57 C.C.P.A. at 1027.

Apparently, and without a reasoned supporting argument, the Examiner assumes *sub silentio* that color is a surrogate for "purity" in the general assay sense (*e.g.*, 98% to 99% assay), with no regard for the possibility that removal of a specific yellowness-causing impurity led to Applicant's white and crystalline venlafaxine and further without regard to fact that color depends on factors other than assay. In this respect, the Examiner takes official notice, relying on its own knowledge, as to the cause of the yellowness in the venlafaxine in the '555 publication. Whether the lack of color in Applicants' novel venlafaxine is caused by a low general purity or by a specific impurity, the removal of which results in the whiteness of the product or whether color *ipso facto* equates with purity, cannot be said to be "capable of instant and unquestionable demonstration as to defy dispute." *See In re Ahlert*, 424 F.2d at 1091.

Moreover, according to the Code of Federal Regulations:

> When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference **must be supported, when called for by the applicant, by the affidavit of such**

> **employee**, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.

37 C.F.R. § 1.104(d)(2) (emphasis added).

Applicants have previously requested that the Examiner provide a reference that teaches or suggests how white crystalline venlafaxine can be obtained, or submit a declaration to support its contention that white crystalline venlafaxine is *prima facie* obvious as a purer assay of the venlafaxine in the '555 publication. *See* June 27, 2005 Amendment, p. 14. However, the Examiner, seeking to rely upon the chemical theory that color is merely an indicia of general purity to establish its *prima facie* case of obviousness, has provided no evidentiary support for the existence and meaning of such a theory. *See In re Mills*, 281 F.2d at 223-24. Instead, the Examiner's rejection is either conclusion based on undisclosed and undocumented knowledge within the ken of the Examiner, or a conclusion "predicated on nothing more than the 'legal presumption' as authority for which it cites" to *Ex parte Gray*, 10 U.S.P.Q.2D (BNA) 1922 (B.P.A.I. 1989). *See In re Mills*, 281 F.2d at 224 ("The 'legal presumption' as here applied by the board precludes making the factual evaluation which a chemist would make in a case such as the present."). "Necessarily it is facts appearing in the record, **rather than prior decisions in and of themselves**, which must support the legal conclusion of obviousness under 35 USC 103." *In re Cofer*, 354 F.2d 664 (C.C.P.A. 1966) (emphasis added).

"The standard of review applied to findings of fact is the 'substantial evidence' standard under the Administrative Procedure Act (APA)." *MPEP* § 2144.03; *In re Lee*, 277 F.3d 1338, 1342-1345 (Fed. Cir. 2002) ("'Common knowledge and common sense,' even if assumed to derive from the agency's expertise, do not substitute for authority when the law requires authority."). Applicants do not dispute that there is substantial technical expertise within the Examining Corps. But the MPEP expressly articulates the guidelines under which official notice

may be taken, stating specifically that when relying upon a chemical theory, the Examiner "must provide evidentiary support for the existence and meaning of that theory." *MPEP* §2144.03(B). Here, the Examiner relies on the "theory" that the color of a compound is a surrogate for the general purity (assay) of the compound. Because the Examiner has provided no evidentiary support, either by way of citation or Examiner's Affidavit, for its bald assertion that there is an inherent nexus between color and purity in the general assay sense, Applicants submit that the "substantial evidence" standard has not been met, and that the Examiner's rejection is therefore improper and should be reversed.

As illustrated above, the presumption that color is an inherent indicia for purity cannot be said to be common knowledge "capable of such instant and unquestionable demonstration as to defy dispute." *See In re Ahlert*, 424 F.2d at 1091. Not only is it pure speculation taken by official notice and not supported by **any** evidence, much less "substantial evidence" as required by the Administrative Procedure Act, but it is also **factually erroneous**, as Applicants have demonstrated with the above examples.

## CONCLUSION

Applicants assert that rejection as *prima facie* obvious of a claim allegedly drawn to a more "pure" form of a known compound is appropriate only if "pure" or "purity" denotes purity in the general sense of assay. The Office has erred legally and factually by equating color and general purity in the sense of assay. Applicants have presented theoretical discussion and practical examples showing that one skilled in the art would not have taken a linkage between color and purity as a given.

Because the general purity ↔ color linkage asserted by the Office is far from beyond dispute, it is improper and unlawful for the Office to take official notice of this putative linkage without proffering the required support, which was expressly requested by Applicants.

There are bald assertions but no discussion in the record to support the Office's position that Applicants crystalline white venlafaxine is merely a more pure form [read higher assay form] of the gummy yellow solid of the '555 publication. Because the Office has failed to present a factual or technically sound basis for linking color and assay, the Office fails to make out a case of *prima facie* obviousness against the claims on appeal.

Applicants earnestly argue that nothing in the art of record – alone or in combination with art in the ken of the skilled artisan of the day – teaches or suggests crystalline white venlafaxine or teaches or suggests a method of obtaining it with a reasonable expectation of success. The prospects of obtaining an undesirable yellow gum would suggest to the skilled artisan that they leave venlafaxine alone.

For the foregoing reasons, Claims 1 and 2 cannot be *prima facie* obvious in light of the '555 publication. Claims 95-98, which are product-by-process claims directed to white crystalline venlafaxine, are therefore also non-obvious. Applicants respectfully submit that the rejection of Claims 1, 2 and 95-98 under 35 U.S.C. § 103 is improper and should be reversed.

## REQUEST FOR EXTENSION OF TIME

Applicants respectfully request a five-month extension of time in which to file this Appeal Brief in connection with its Notice of Appeal received by the Office on July 1, 2005. The five-month extended period expires on February 1, 2006.

**AUTHORIZATION TO DEBIT DEPOSIT ACCOUNT**

The Office is further authorized to charge any additional fees required in relation to this paper, or credit any over payments under 37 C.F.R. § 1.16 or § 1.17 to **Kenyon & Kenyon LLP, deposit account 11-0600**, referencing Attorney Docket No. **01662/054902**.

Respectfully submitted,

KENYON & KENYON LLP

Date: May 15, 2006

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## CLAIMS APPENDIX

1. A crystalline venlafaxine base wherein the venlafaxine base is in the form of white crystals.

2. A crystalline venlafaxine base according to claim 1, wherein the venlafaxine base has a purity of greater than about 99.3%.

95. White crystalline solid venlafaxine base prepared by a method comprising the steps of:

a) providing a solution of venlafaxine hydrochloride in water,

b) combining the solution of venlafaxine hydrochloride with sodium hydroxide,

c) extracting the combination with an organic solvent to obtain extract,

d) drying the extract,

e) evaporating the extract to obtain a residue,

f) combining the residue with an alkane, and

g) crystallizing venlafaxine base that is a white crystalline solid from the combination of residue and alkane.

96. The white crystalline solid venlafaxine base of claim 95 wherein the organic solvent of step c) is selected from ethyl acetate, heptane, hexane, and mixtures of any of them.

97. The white crystalline solid venlafaxine base of claim 95 having a purity of at least about 98% by weight.

98. The white crystalline solid venlafaxine base of claim 97 having a purity of at least about 99% by weight.

## EVIDENCE APPENDIX

1. International publication No. WO 00/32555 (the '555 publication). The '555 publication was cited as prior art in the Office Actions of February 25, 2004 and December 28, 2004.

2. *BASF Aktiengesellschaft* FAQ, http://www2.basf.de/en/intermed/nbd/products/ionicliquids/faq.htm?id=V00-cK1th82Yqbw22XQ#2c. This reference is the basis for Applicants' arguments relating to "purity" and "assay" on p. 10 of the June 27, 2005 Amendment.

3. *Fisher Scientific International*, Frequently Asked Questions, https://www1.fishersci.com/support/faq/faq_chem.jsp. This reference is the basis for Applicants' arguments concerning "purity" and "assay" on p. 10 of the June 27, 2005 Amendment.

4. *AJS Gems Gem Library*, www.ajsgems.com/GemLibrary/Ruby.htm. This was referred to as "Tab A" in Applicants' June 27, 2005 Amendment.

5. Gordon et al., *Crystals*, The Natural History Museum, p. 13 (2004). This was referred to as "Tab A" in Applicants' June 27, 2005 Amendment.

6. International publication No. WO 02/102382. This reference was relied upon by Applicants its June 27, 2005 Amendment.

7. Smith et al., *Application of Two-Dimensional 13C Solid-State NMR to the Study of Conformational Polymorphism*, J. AM. CHEM. SOC., 11710-11713 (1998). This was referred to as "Tab B" in Applicants' June 27, 2005 Amendment.

8. *In re Cofer*, 354 F.2d 664 (C.C.P.A. 1966). This was the primary case was relied upon by Applicants its June 27, 2005 Amendment.

## RELATED PROCEEDINGS APPENDIX

Not Applicable.